Remarks/Arguments:

I. Claim Status

Claims 15-17 are withdrawn from consideration. Claims 3, 7 and 12 have been cancelled. Claim 1 has been amended to recite that the suspension is an aqueous suspension, that at least 70% of the glucocorticosteroid is in the form of a suspension during heating, and that at least one surfactant is present in the aqueous suspension during heating. Claims 2 and 13 have likewise been amended to recite that at least 70% of the glucocorticosteroid (or budesonide) is in the form of a suspension during heating and that at least one surfactant is present in the aqueous suspension during heating. Support for these amendments is found at paragraphs [0029] and [0037] of the specification (paragraph numbers, as used herein, refer to the paragraph numbers set forth in published application US 2008/0139519); no new matter has been introduced. As a result, Claims 1, 2, 4-6, 8-11, 13 and 14 remain pending and under examination.

II. Interview

Applicants express their appreciation to Primary Examiner Fetterolf and Examiner Ricci for the courtesy of the in-person interview conducted with Applicants' legal representatives on November 18, 2009.

III. Rejection under 35 USC § 102(b)

Claims 1-7 and 9 were rejected as allegedly anticipated by McAffer *et al.* (US2003/0103864; hereafter, "the McAffer reference"). Applicants respectfully request reconsideration and withdrawal of the rejection in view of the claim amendments and the following remarks.

The rejection stated:

7. *McAffer et al* teach a method for the sterilization of budesonide (i.e., a glucocorticosteriod, more specifically a labile glucocorticosteroid as recited by instant claims 1, 2 and 9) in a suspension further comprising polysorbate 80 (i.e., a surfactant as recited by instant claim 7) comprising autoclaving (as recited by instant claim 5) at 121°C (as recited by instant claim 4) for 15 minutes (as recited by instant claim 6) (Paragraph 0057). Furthermore, *McAffer et al* disclose that "the polysorbate surfactant was filter sterilized into a sterile vessel. To this vessel micronized budesonide was added aseptically... After addition the budesonide lay on top of the filtered polysorbate. Mixing was achieved by the use of a high shear mixing shaft. Twenty to twenty-five minutes of continuous mixing were required for the budesonide to go completely into suspension" (Paragraph 0038). As such, *McAffer et al* teach the method wherein the budesonide is used in a sufficient amount such that at least 50% (more specifically, at least 60% - as recited by instant claim 3) of the glucocorticosteroid is in the form of a suspension during heating. Accordingly, instant claims 1-7 and 9 are anticipated.

Anticipation under 35 USC §102 requires that the reference teach every aspect of the claimed invention either explicitly or implicitly. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). To anticipate, a prior art reference must not only teach all the claim elements, but also the claimed arrangement or combination of those elements. *NetMoneyIN v. Verisign*, 545 F.3d 1359, 1369 (Fed. Cir. 2008).

Applicants respectfully submit that the McAffer reference discloses several different processes, but fails to disclose <u>any</u> process that combines all of the elements of Applicants' claim 1.

The rejection pointed to a method of sterilizing budesonide disclosed at paragraph [0057] of the McAffer reference. That experiment discloses a temperature of 121° C and a heating time of 15 minutes. But the process employed in that McAffer reference experiment still differs from the claimed process. Paragraph [0057] of the McAffer reference is reproduced in its entirety below.

> **[0057]** To evaluate both the effects of dry heat and any potential benefits of autoclaving budesonide as a concentrated dispersion in polysorbate 80, samples of budesonide were treated with dry heat under standard atmospheric conditions at different temperatures for periods of 15 minutes. Subsequently the samples were dispersed in polysorbate 80 and autoclaved for 15 minutes at 121° C. A control sample was prepared by dispersing budesonide in polysorbate 80 and autoclaving at 121° C. for 15 minutes with no prior dry heating. This control sample was prepared to allow for the effect of the initial dry heating step to be evaluated.

Thus, McAffer's paragraph [0057] experiment taught sterilization of budesonide by autoclaving a concentrated dispersion of budesonide in polysorbate 80 for 15 minutes at 121°C (with, and also without, a prior dry heating step). This experiment does not teach the claimed process, which requires heating an aqueous suspension of a glucocorticosteroid.

The rejection also pointed to paragraph [0038] of the McAffer Reference, alleging that the teaching therein that "twenty to twenty-five minutes of continuous mixing were required for the budesonide to go completely into suspension." The section of the McAffer reference that includes paragraph [0038] is reproduced below.

> Preparation of a "Clean" Budesonide Formulation
>
> **[0036]** Preparation of a clean suspension of budesonide particles for use in a nebulizer in which the final formulation comprises budesonide, a polysorbate surfactant, water and preservatives was carried out as follows.
>
> **[0037]** A bulk solution consisting of all the components of the final formulation except budesonide and the surfactant was sterilized by passage through a 0.2 μm filter (0.1 μm is also suitable). The filtered solution was held at room temperature and a pressure of approximately 2 bar in a sterile vessel.
>
> **[0038]** In the enclosed environment of a container cabinet, the polysorbate surfactant was filter sterilized into a sterile vessel. To this vessel micronized budesonide was added aseptically. The particle size of the budesonide was such that 100% of the particles were less than 10 μm and 95% of the particles were less than 5 μm in diameter. After addition the budesonide lay on top of the filtered polysorbate. Mixing was achieved by the use of a high shear mixing shaft. Twenty to twenty-five minutes of continuous mixing were required for the budesonide to go completely into suspension. After mixing was complete the mixing shaft was rinsed with sterile water and the vessel was sealed.

Again, in this part of the McAffer reference disclosure, the suspension that is being prepared is clearly a suspension of the budesonide in the polysorbate surfactant. Paragraph [0038] thus does not teach the claimed process, at least because the claimed process requires heating an aqueous suspension of a glucocorticosteroid. In addition, the experiment of paragraph [0038] could not anticipate because it expressly did not teach

heating, and did not even teach a *sterilization* process. The experiment described in McAffer's paragraph [0038] was a "Preparation of a 'Clean' Budesonide Formulation." The McAffer reference clearly distinguishes between processes that "clean" and processes that "sterilize:"

> **[0002]** Previously it was acceptable for drugs intended for use in nebulizers to be prepared under "clean" conditions. Recently, however, the U.S. FDA has implemented a requirement for all nebulizer solutions to be sterile.
>
> **[0003]** In the light of the U.S. FDA decision it is necessary to produce sterile suspension drugs in the U.S. This is emphasised by problems which have resulted from the use of "clean" suspensions. Multidose formulations made under "clean" conditions in which the composition was in a "preserved" state were previously acceptable in the U.S. However such preserved and clean-filled formulations have caused fatalities in the U.S. due to contamination.

Paragraph [0073] of the McAffer reference discloses preparation of two formulations (02401D and 02401E) of budesonide for evaluating McAffer's "High Temperature Short Time" (HTST) sterilization process. One of those formulations, designated 02401E, was an aqueous formulation. But neither of the formulations embraces the concentration range of independent claim 2. Paragraph [0073] of the McAffer Reference is reproduced below:

> **[0073]** Two samples of budesonide suspension were prepared for evaluation. One sample was prepared with little care taken to protect the sample from contamination by micro-organisms present on equipment used for preparation or from the surrounding atmosphere (02401D). The other using good aseptic technique (02401E). Sample 02401D was prepared as a concentrated formulation comprising budesonide, polysorbate 80 and water, whereas 2401E was a fully formulated composition also comprising further excipients. The formulations of these samples are detailed in Table 5.

As shown in Table 5, McAffer's two disclosed formulations contained budesonide at concentrations of 1.31 mg/mL and 0.25mg/mL. In contrast, independent claims 1, 2 and 13, as herein amended, each recite that "at least 70% of the glucocorticosteroid is in the form of a suspension during heating." The solubility of budesonide at the sterilization temperature is such that the budesonide concentration must be at least about 23 mg/mL in order for the claim limitation of "at least 70% of the glucocorticosteroid is in the form of a suspension" to be met. Such a minimum concentration is clearly much higher than the budesonide concentrations contemplated by the McAffer reference.

Thus, none of the processes taught by the McAffer reference disclose all of the elements of the claimed process. Based on the discussion above, Applicants respectfully request that the Examiner reevaluate and withdraw the anticipation rejection.

IV. Rejection of Claims 1-6 and 9-14 under 35 USC §103(a)

Claims 1-6 and 9-14 were rejected as allegedly obvious over Gentile *et al.* (US 2006/0140816 and EP 1454636; hereafter, "the Gentile reference"). This rejection has been rendered moot by the amendment of independent Claims 1, 2 and 13 (from which all the remaining pending claims depend, directly or indirectly) to include the subject matter of Claim 7 (now cancelled). Claim 7, which had specified that the suspension further comprises a surfactant, was not rejected as allegedly obvious over the Gentile reference.

V. Rejection of Claims 7 and 8 under 35 USC §103(a)

Applicants traverse the rejection of Claims 7 and 8 as allegedly obvious over the Gentile reference in further view of Karlsson et al. (US 6,392,036; hereafter, "the Karlsson reference") and McAffer reference. The rejection of Claim 7 has been rendered moot by the cancellation of this claim. However, since the subject matter of Claim 7 has now been incorporated into the remaining claims that are still pending in this application, Applicants ask that the Office evaluate the patentability of these claims in view of the following remarks.

Applicants' invention is concerned with the problem of how to effectively sterilize labile glucocorticosteroids while not adversely affecting the desirable characteristics of such drugs. Acceptable solutions to this problem have been difficult to realize, as explained in Paragraphs [0003] and [0004] of Applicants' specification:

> **[0003]** Methods are needed for the preparation of sterile products for patient use. However, the problem associated with many sterilization procedures is that the process often results in unfavorable changes in the drug profile. These changes in the drug profile can range from loss of activity, to increased degradation products being created, or possible alteration of the chemical or physical characteristics of the compound sterilized. These problems are especially pronounced when glucocorticosteroids are sterilized.
> **[0004]** Sterilization of materials relies on the input of sufficient energy to be lethal to any potential microbial contamination. Numerous methods including heat, radiation, and chemicals have been proposed for the sterilization of glucocorticosteroids. However, to date these methods often result in the excess production of degradants or a loss of activity for the glucocorticosteroid being sterilized. Additionally, as in the case of glucocorticosteroid suspension formulations for metered dose inhalation, the commonly used sterilization procedures often results in unacceptable changes to drug particle size.

The McAffer reference (Paragraph [0005]) confirms the challenges associated with sterilizing suspensions of drugs intended for use in nebulizers:

> [0005] The sterilization of suspensions raises particular problems. The desired biological activity of the formulation commonly requires that the diameter of particles of the drug lies within a narrow range (typically less than 5 micrometers). The standard means of sterilization, that is the raising of the temperature of the formulation to 121° C. for 15 minutes, frequently destroys one or more of the components of the formulation. In addition this treatment results in the clumping or agglomeration of the drug particles in the suspension such that the efficacy of the resulting product is impaired or abolished.

Likewise, the Gentile reference (Paragraphs [0002] to [0007]) teaches the criticality of selecting and controlling the sterilization treatment conditions so as to avoid altering the physical and chemical characteristics of the active drug substance:

> [0002] The process for sterilizing powdered forms of water insoluble drug substance to be suspended into a sterile aqueous vehicle suitable for the pulmonary administration, such as non-electrolyte corticosteroids, glucocorticoids and the like, is still a critical process. The major problems are related to the high temperatures of the sterilization process and to the consequent thermal instability of the drug substance that frequently leads to degradation with modification of the impurities profile and of the physico-chemical characteristics of the drug.
>
> [0003] For solid drug substances suitable for inhalation delivery to be suspended in aqueous formulations, the particle size distribution, as well as its preservation during the shelf-life of the finished product, are particularly crucial parameters.
>
> [0004] The particle size influences, in fact, the distribution of the drug into the lung and, as a consequence, the activity and effectiveness of the drug itself. It is generally accepted that the mean diameter of the particles in a formulation for inhalation delivery must be less than 10 microns, preferably about 5 microns or less.
>
> [0005] Solid non-electrolyte corticosteroids, steroids as well as non-steroid drugs for use in aqueous suspensions are usually sterilized in different ways, for example by exposure to gases, or by aseptic crystallisation, drug heat sterilization, or by β and γ irradiation.
>
> [0006] The sterilizing treatment can cause adverse physical and chemical changes of the drug substance and all parameters have to be checked and investigated in the preliminary phase of the process development.
>
> [0007] In the case of drug substances intended for inhalation use, in addition to the control of the physical and chemical stability of the sterilized drug, it is then crucial to prevent any unacceptable change in particle size due to possible recrystallization of the drug, which is consequent to many known sterilization methods.

The sterilization of labile glucocorticosteroids thus is recognized as a challenging and unpredictable technical field. Seemingly minor changes or differences in sterilization conditions or techniques can lead to significantly different results.

However, as explained in paragraphs [0028] and [0029] of their specification, Applicants have now found an effective method for heat sterilization of labile glucosteroids:

> **[0028]** An aspect of the invention provides a method for the heat sterilization of a labile glucocorticosteroid. The method of this aspect comprises the step of exposing to moist heat a suspension of a labile glucocorticosteroid for a sterilizing-effective time. The applicant has found that an undesirable increase in the particle size of the glucocorticosteroid as well as the formation of unwanted by-products may be avoided by careful restriction of the sterilization parameters and the nature of the glucocorticosteroid. The glucocorticosteroid must have a sufficiently low solubility in the suspending solvent and be employed in a sufficiently high concentration that only a minor portion of the glucocorticosteroid dissolves in the suspending solvent. In this manner, degradation of the glucocorticosteroid results in minimal by-products and recrystallisation of the glucocorticosteroid on cooling leading to an undesirable increase in particle size may be avoided.
>
> **[0029]** A balance is required between the Solubility of the glucocorticosteroid and the amount of the glucocorticosteroid used per unit of solvent such that at least 50% of the glucocorticosteroid is suspended in the solvent. For example, for budesonide, at the sterilizing temperatures used herein the water solubility is about 7 mg/ml. Therefore, using 15 mg of budesonide per 1 mg water provides 53% of budesonide as a suspension. Preferably at least 60% of the glucocorticosteroid is suspended in the solvent although this value could be at least 70% or at least 80%.

In the Office Action, the Examiner notes that the Gentile reference teaches a glucocorticoid sterilization process which comprises heating an aqueous suspension of a glucocorticosteroid and water wherein the glucocorticoid:water ratio is preferably between about 3:100 (about 30 mg/ml) to 10:100 (about 100 mg/ml). However, the water solubility of different glucocorticosteroids varies depending upon the chemical structure of the particular glucocorticosteroid. The Gentile reference does not distinguish between different glucocortisteroids with respect to the glucocorticosteroid:water ratio that might be preferred. In other words, the "about 3:100...to 10:100" range is preferred regardless of the glucocorticosteroid being sterilized. As mentioned above, however, Applicants have now discovered that favorable results are obtained (avoidance of the formation of undesirable by-products and an increase in particle size) when the amount of water relative to the particular glucocorticosteroid being sterilized is selected such that at least 70% of the glucocorticosteroid remains in suspension during heating. Nothing in the Gentile reference, or in any of the other cited references, would have made it obvious to a person of ordinary

skill in the art to control the proportion of glucocorticosteroid staying in suspension such that it is maintained above a certain minimum level.

Applicants further note that the pending claims have been amended to recite that at least one surfactant is present in the aqueous suspension during heating. Applicants respectfully submit that such a method for sterilizing a labile glucocorticosteroid would not have been obvious to a person of ordinary skill in the art from the Gentile, Karlsson and McAffer references, either alone or in combination.

The Gentile reference discloses a process for the steam sterilization of glucocorticoids using an aqueous suspension of the glucocorticoid. According to the Gentile reference, the process comprises "heating a mixture of water and micronized beclomethasone at a temperature ranging between 100° and 130° C for a time sufficient to sterilise the mixture with a minimum S.A.L. ...of 10^{-6}, the mixture being a mixture of beclomethasone and water only" (Paragraph [0017], emphasis added). As described in Example 3 of the Gentile reference, a surfactant may be formulated together with an aqueous beclomethasone suspension after sterilization of the suspension has been carried out. Paragraphs [0008] to [0010] of the Gentile reference describe the problems reportedly encountered when steam sterilization of corticosteroids is attempted in the presence of substances other than water and the corticosteroid. An ordinarily skilled worker thus would have been discouraged from altering the Gentile reference process to include a surfactant in the aqueous corticosteroid suspension when such suspension is being sterilized by heating.

The Examiner notes that the Karlsson reference teaches that "[t]o obtain an efficient dispersion of the glucocorticosteroid particles in the suspension, a surfactant may be used" (Column 5, Lines 21-24). However, the Karlsson reference is concerned with dry sterilization of powdered forms of glucocorticosteroid. See, for example, Column 1, Lines 8 and 9, Column 2, Lines 42-45 and 50-53, and the Examples. It is only after such dry sterilization that the glucocorticosteroid is formulated into an aqueous suspension which may contain surfactant. See Column 6, Lines 34-46.

Notably, the Karlsson reference teaches (Column 2, Lines 24-32) that sterilizing aqueous suspensions of glucocorticosteroids is problematic:

> We have also found that attempts at terminal sterilization of the pharmaceutical formulations, especially suspensions, e.g. aqueous suspensions, of glucocorticosteroids have all proved unsatisfactory. Such suspensions can not normally be sterilized by sterile filtration as most of the particles of glucocorticosteroid will be retained on the filter. We have also shown that moist heat sterilization, e.g. steam treatment of glass vials containing the product, leads to an unacceptable change in particle size.

Thus, a worker of ordinary skill in the art would not have found it obvious to modify the Karlsson reference by sterilizing a glucocorticosteroid in the form of an aqueous suspension also containing surfactant, as he or she would not have reasonably expected the outcome of such a modification to be favorable.

The teachings of the McAffer reference have been previously discussed in detail in connection with the rejection of Claims 1-7 and 9 under 35 U.S.C. §102(b). As noted in the earlier discussion, the McAffer reference fails to disclose a method for sterilizing a labile glucocorticosteroid wherein moist heat is applied to an aqueous suspension of a labile glucocorticosteroid for a sterilizing-effective time, with at least 70% of the glucocorticosteroid being in the form of a suspension during heating and at least one surfactant being present in the aqueous suspension during heating. The McAffer reference does disclose (Paragraph [0073] and Table 5) the processing of two formulations containing relatively low concentrations of budesonide, together with polysorbate 80 and water. However, in view of the recognized challenges and unpredictability associated with the glucocorticosteroid sterilization art (as acknowledged by the McAffer, Karlsson and Gentile references), an ordinarily skilled worker would not have found it obvious that much more highly concentrated glucocorticosteroid suspensions could be successfully sterilized with minimal impact on other critical properties and characteristics of the sterile glucocorticosteroid suspension thereby obtained. In particular, Applicants have unexpectedly discovered that an undesirable increase in the particle size of the glucocorticosteroid as well as the formation of unwanted by-products may be avoided by carrying out sterilization under the particular conditions recited in the pending claims. Such favorable results were surprising in view of the recognition in the field that glucocorticosteroid sterilization using a wet steam process can lead to significant decreases in active ingedient content (see Page 11, Lines 1-12, of WO 00/25746, a copy of which was included with the Information Disclosure Statement submitted December 4, 2009) or unfavorable changes in particle size (see Column 1, Lines 33-44, of the Karlsson reference).

VI. Non-statutory Double Patenting Rejection

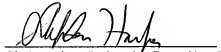
Claims 1-4, 6, 7 and 9-13 have been provisionally rejected for obviousness-type double patenting over claims 1, 3, 6, 9, 10, 13 and 15 of copending U.S. Patent Application 11/667,872.

Claim 1 as amended, recites a glucocorticosteroid sterilization process wherein at least 70% of the glucocorticosteroid is in the form of an aqueous suspension during heating and wherein at least one surfactant is present in the suspension during heating. The claims

cited in the reference cited for the double patenting rejection recite neither a surfactant nor any required level of suspension. Accordingly, in light of the amendment herein, Applicants respectfully request that the examiner reconsider and withdraw the obviousness-type double patenting rejection.

In light of the discussion above and the claim amendments herein, Applicants believe that all claims in this Application are in condition for allowance.

Respectfully Submitted,



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